

WEST Search History

DATE: Friday, June 02, 2006

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|--------------------------|---------------------------|---|----------------------------|
| | | <i>DB=PGPB,USPT; PLUR=YES; OP=OR</i> | |
| <input type="checkbox"/> | L8 | L7 and (neutrophil? or PMN) | 109 |
| <input type="checkbox"/> | L7 | L6 and apoptosis | 538 |
| <input type="checkbox"/> | L6 | (inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC or PI3 adj kinase) | 913 |
| | | <i>DB=EPAB,JPAB,DWPI; PLUR=YES; OP=OR</i> | |
| <input type="checkbox"/> | L5 | ((inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC or PI3 adj kinase)) | 63 |

END OF SEARCH HISTORY

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DATE: Friday, June 02, 2006

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| | | <i>DB=PGPB,USPT; PLUR=YES; OP=OR</i> | |
| <input type="checkbox"/> | L4 | MURPHY adj FINBARR | 3 |
| <input type="checkbox"/> | L3 | HAYES adj IAN | 6 |
| <input type="checkbox"/> | L2 | HAYES adj IAN | 6 |
| <input type="checkbox"/> | L1 | SEERY adj LIAM | 4 |

END OF SEARCH HISTORY

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| NEWS | 6 | FEB 22 | Updates in EPFULL; IPC 8 enhancements added |
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| NEWS | 10 | APR 03 | New IPC 8 fields and IPC thesaurus added to PATDPAFULL |
| NEWS | 11 | APR 03 | Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL |
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| NEWS | 13 | APR 12 | LINSPEC, learning database for INSPEC, reloaded and enhanced |
| NEWS | 14 | APR 12 | Improved structure highlighting in FQHIT and QHIT display in MARPAT |
| NEWS | 15 | APR 12 | Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected |
| NEWS | 16 | MAY 10 | CA/CAPLUS enhanced with 1900-1906 U.S. patent records |
| NEWS | 17 | MAY 11 | KOREAPAT updates resume |
| NEWS | 18 | MAY 19 | Derwent World Patents Index to be reloaded and enhanced |
| NEWS | 19 | MAY 30 | IPC 8 Rolled-up Core codes added to CA/CAPLUS and USPTAFULL/USPAT2 |
| NEWS | 20 | MAY 30 | The F-Term thesaurus is now available in CA/CAPLUS |
| NEWS EXPRESS | | | FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/ |
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=> s (inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC
or PI3 adj kinase)

L1 11 (INOSITOL ADJ 1 ADJ 4 ADJ 5 ADJ TRIPHOSPHATE ADJ 3 ADJ KINASE
ADJ C OR ITPKC OR PI3 ADJ KINASE)

=> inositol adj 1(w)4(w)5(w)triphosphate(w)3(w)kinase(w)C or ITPKC or PI3(w)kinase
INOSITOL IS NOT A RECOGNIZED COMMAND

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=> s inositol adj 1(w)4(w)5(w)triphosphate(w)3(w)kinase(w)C or ITPKC or PI3(w)kinase
L2 9050 INOSITOL ADJ 1(W) 4(W) 5(W) TRIPHOSPHATE(W) 3(W) KINASE(W) C OR
ITPKC OR PI3(W) KINASE

=> s l2 and apoptosis
L3 1756 L2 AND APOPTOSIS

=> s l3 and (neutrophil? or PMN)
L4 42 L3 AND (NEUTROPHIL? OR PMN)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 25 DUP REM L4 (17 DUPLICATES REMOVED)

=> dis ibib abs l5 15-25

L5 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:458227 CAPLUS
DOCUMENT NUMBER: 141:223474
TITLE: Granulocyte apoptosis: who would work with a
'real' inflammatory cell?
AUTHOR(S): Dransfield, I.; Rossi, A. G.
CORPORATE SOURCE: MRC Centre for Inflammation Research, University of
Edinburgh Medical School, Edinburgh, EH8 9AG, UK
SOURCE: Biochemical Society Transactions (2004), 32(3),
447-451
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The neutrophil granulocyte is a key factor in
cellular innate defense mechanisms against infection or tissue damage.
Granulocyte apoptosis is now acknowledged to have a critical role

in progression of inflammatory responses. Granulocytes are preprogrammed to die with important physiol. mechanisms for non-inflammatory clearance. Shutdown of secretory capacity represents an important aspect of the program of biochem. events that accompany neutrophil apoptosis together with surface mol. changes that serve to identify apoptotic cells as targets for phagocytic removal. Defining the underlying regulatory mechanisms together with the changes in patterns of gene/protein expression associated with granulocyte death remains a challenge. Use of novel strategies for inducing cell death will allow biochem. approaches to dissect the underlying pathways. Although study of granulocyte cell death has especial difficulties when compared with other cell types, there are clearly potential benefits for new therapeutic approaches to treat inflammatory diseases.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 6

ACCESSION NUMBER: 2005:130748 BIOSIS
DOCUMENT NUMBER: PREV200500122019
TITLE: The roles of PI3-kinase and PKC in the signaling pathways of human neutrophil apoptosis induced by Entamoeba histolytica.
AUTHOR(S): Sim, Seobo [Reprint Author]; Shin, Myeong Heon; Kim, Kyeong Ah; Ryu, Jae-Sook
CORPORATE SOURCE: Dept ParasitolInst Trop MedBrain Korea 21 Project Med Sci, Yonsei Univ, Seoul, 120749, South Korea
SOURCE: Journal of Leukocyte Biology Supplement, (2004) No. 2004, pp. 50. print.
Meeting Info.: 37th Annual Meeting of the Society for Leukocyte Biology "Host Response to Pathogens". Toronto, ON, Canada. October 21-23, 2004. Society for Leukocyte Biology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Apr 2005
Last Updated on STN: 1 Apr 2005

L5 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:454493 CAPLUS
DOCUMENT NUMBER: 139:31825
TITLE: Nucleic acid and polypeptide sequences for human 55-kilodalton phosphatidylinositol 3-kinase and their diagnostic and therapeutic uses for apoptosis
INVENTOR(S): Hayes, Ian; Cotter, Thomas; Murphy, Finbarr; Seery, Liam
PATENT ASSIGNEE(S): Eirx Therapeutics Limited, Ire.
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2003048361 | A2 | 20030612 | WO 2002-GB5547 | 20021206 |
| WO 2003048361 | A3 | 20040318 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002347368 A1 20030617 AU 2002-347368 20021206
PRIORITY APPLN. INFO.: GB 2001-29377 A 20011207
GB 2002-831 A 20020115
WO 2002-GB5547 W 20021206

AB The invention provides a method for detecting **apoptosis** in a cell comprising detecting an alteration in any one of: (i) a phosphatidylinositol kinase (p55PIK) polypeptide having an amino acid sequence as set out in SEQ ID NO:1; (ii) a polypeptide having at least 80 % homol. with (i); (iii) a nucleic acid encoding a polypeptide having the sequence set out in (i) or (ii); (iv) a nucleic acid which hybridizes under stringent conditions to the sequence set out in (iii); or (v) the complement of (iii) or (iv). The invention accordingly provides a method of modulating **apoptosis** by modulating p55PIK gene expression and a method for identifying genes associated with p55PIK gene expression and thus identifying other genes associated with **apoptosis**. The invention also provides a novel nucleic acid sequence encoding the promoter region for p55PIK gene. The invention further claims methods and compns. such as p55PIK siRNA, p55PIK antisense nucleic acids, and microarrays for use in identifying drug candidates that modulate p55PIK expression or activity. The methods are claimed for therapeutic use in treatment of cancer, inflammation, and neurodegenerative diseases. In the examples of the invention, the fungal metabolite gliotoxin was identified as an inhibitor of granulocyte macrophage colony-stimulating factor (GM-CSF)-mediated inhibition of human **neutrophil apoptosis**. An increase in p55PIK mRNA in GM-CSF-induced **neutrophil** survival is blocked by gliotoxin. The p55PIK gene and signal transduction-associated genes were differentially expressed in microarray expts. of **neutrophil apoptosis** and survival.

L5 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:398123 CAPLUS

DOCUMENT NUMBER: 140:35353

TITLE: Alteration of constitutive **apoptosis** in **neutrophils** by quinolones

AUTHOR(S): Azuma, Yasutaka; Ohura, Kiyoshi

CORPORATE SOURCE: Department of Pharmacology, Osaka Dental University, Hirakata, Osaka, 573-1121, Japan

SOURCE: Inflammation (Dordrecht, Netherlands) (2003), 27(3), 115-122

CODEN: INFLD4; ISSN: 0360-3997

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Neutrophils** constitutively undergo **apoptosis** at sites of infection. The process of **apoptosis** controls inflammatory responses of **neutrophils**. However, little is known about the abilities of quinolones, which are often administered to patients showing infection disease, on constitutive **apoptosis** of **neutrophils**. The aim of this study is to evaluate abilities of quinolones on constitutive **apoptosis** of **neutrophils**. Tosufloxacin delayed **neutrophil** death and delayed **neutrophil apoptosis**. In contrast, ofloxacin, lomefloxacin, fleroxacin, sparfloxacin, and levofloxacin markedly promoted **neutrophil** death without affecting **neutrophil apoptosis**. Inhibitors of phosphoinositide 3-kinase (PI3K) and p38 mitogen-activated protein kinase (MAPK) attenuated the delay of **neutrophil apoptosis** by tosfloxacin, resp. However, an inhibitor of extracellular-signal-related kinase did not alter the delay

of neutrophil apoptosis by tosylfloxacin. Moreover, tosylfloxacin increases the expression of p85, p110 β , and Akt protein in neutrophils. These results suggest that tosylfloxacin may delay neutrophil apoptosis via activation of PI3K/Akt and/or p38 MAPK, and the other quinolones may promote neutrophil death without affecting their apoptosis.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 25 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002477246 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12239175
TITLE: Role of PI3-kinase-dependent Bad phosphorylation and altered transcription in cytokine-mediated neutrophil survival.
AUTHOR: Cowburn Andrew S; Cadwallader Karen A; Reed Benjamin J; Farahi Neda; Chilvers Edwin R
CORPORATE SOURCE: Respiratory Medicine Division, Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, United Kingdom.
SOURCE: Blood, (2002 Oct 1) Vol. 100, No. 7, pp. 2607-16. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20 Sep 2002
Last Updated on STN: 19 Dec 2002
Entered Medline: 5 Dec 2002
AB Phosphoinositide 3-kinase (PI3-kinase)-dependent phosphorylation of the proapoptotic Bcl-2 family member Bad has been proposed as an important regulator of apoptotic cell death. To understand the importance of this pathway in nontransformed hematopoietic cells, we have examined the effect of survival cytokines on PI3-kinase activity and Bad expression and phosphorylation status in human neutrophils. Granulocyte macrophage-colony-stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-alpha) both reduced the rate of apoptosis in neutrophils cultured in vitro for 20 hours. Coincubation with the PI3-kinase inhibitor LY294002, which in parallel experiments abolished GM-CSF-primed, fMLP-stimulated superoxide anion production and GM-CSF-stimulated PtdIns(3,4,5)P(3) accumulation, inhibited the GM-CSF and TNF-alpha survival effect. In contrast, the MAP kinase kinase (MEK1/2) inhibitor PD98059 and the protein kinase A inhibitor H-89 had only a marginal effect on GM-CSF-mediated neutrophil survival. GM-CSF substantially increased Bad phosphorylation at Ser112 and Ser136 and increased the cytosolic accumulation of Bad. GM-CSF also regulated Bad at a transcription level with a marked decrease in mRNA levels at 4 hours. TNF-alpha caused a biphasic effect on the rate of morphologic apoptosis, which corresponded to an early increase, and a late inhibition, of Bad mRNA levels. LY294002 inhibited GM-CSF- and TNF-alpha-mediated changes in Bad phosphorylation and mRNA levels. These data suggest that the survival effect of GM-CSF and TNF-alpha in neutrophils is caused by a PI3-kinase-dependent phosphorylation and cytosolic translocation of Bad, together with an inhibition of Bad mRNA levels. This has important implications for the regulation of neutrophil apoptosis in vivo.

L5 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:109306 CAPLUS
DOCUMENT NUMBER: 136:261789
TITLE: Acute endotoxemia prolongs the survival of rat lung

neutrophils in response to
12-O-tetradecanoyl-phorbol 13-acetate
AUTHOR(S): Sunil, Vasanthi R.; Connor, Agnieszka J.; Lavnikova,
Natasha; Gardner, Carol R.; Laskin, Jeffrey D.;
Laskin, Debra L.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Rutgers
University, Piscataway, NJ, 08854, USA
SOURCE: Journal of Cellular Physiology (2002), 190(3), 382-389
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acute endotoxemia is associated with prolonged survival of adherent
neutrophils in the lung vasculature. In the present studies, the
effects of inflammatory mediators on signaling pathways regulating
neutrophil survival were examined. We found that the protein kinase
C activator, 12-O-tetradecanoyl-phorbol 13-acetate (TPA), but not
interferon- γ (IFN- γ), prolonged the survival of adherent
vasculature lung neutrophils from endotoxemic rats, a response
that was correlated with reduced apoptosis. Although endotoxin
administration to rats induced the expression of the anti-apoptotic
protein Mcl-1 in lung neutrophils, TPA had no effect on this
response. Endotoxin administration also induced expression of total p38
and p44/42 mitogen activated protein kinases (MAPK) in neutrophils
, as well as phosphatidyl inositol 3 kinase (PI3K) and its downstream
target protein kinase B (PKB). Treatment of the cells with TPA increased
p38 MAPK expression in cells from both control and endotoxin treated
animals. Cells from endotoxin treated, but not control animals, were
found to exhibit constitutive binding activity of nuclear factor kappa B
(NF- κ B) which was blocked by TPA. In contrast, constitutive
CCAAT/enhancer binding protein (C/EBP) nuclear binding activity evident in
neutrophils from control animals was reduced following endotoxin
administration. Moreover, this response was independent of TPA. These
data suggest that NF- κ B plays a role in TPA-induced signaling
leading to prolonged survival of adherent vascular neutrophils
in the lung during acute endotoxemia.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:541555 CAPLUS
DOCUMENT NUMBER: 137:153784
TITLE: Polysaccharide purified from Ganoderma lucidum
inhibits spontaneous and Fas-mediated
apoptosis in human neutrophils
through activation of the phosphatidylinositol 3
kinase/Akt signaling pathway
AUTHOR(S): Hsu, Ming-Jen; Lee, Shih-Sheng; Lin, Wan-Wan
CORPORATE SOURCE: Department of Pharmacology, College of Medicine,
National Taiwan University, Taipei, Taiwan
SOURCE: Journal of Leukocyte Biology (2002), 72(1), 207-216
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental
Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ganoderma lucidum has been widely used as a remedy to promote health and
longevity in China. The polysaccharide component with a branched
(1 \rightarrow 3)- β -D-glucan moiety from G. lucidum (PS-G) has shown
evidence of enhancement of immune responses and of eliciting anti-tumor
effects. In this study, the authors investigated the effect of PS-G on
neutrophil viability, which is manifested by spontaneous
apoptosis. Annexin V staining and MTT assays reveal that PS-G is
able to inhibit spontaneous and Fas-induced neutrophil

apoptosis, and this effect of PS-G is enhanced by the presence of zVAD (a caspase inhibitor) and GM-CSF. The anti-apoptotic effect of PS-G is diminished by the presence of wortmannin and LY294002 (two PI-3K inhibitors), but is not altered by PD98059 (a MEK inhibitor). Western blotting indicates the stimulating effect of PS-G on Akt phosphorylation and its inhibition of procaspase 3 degradation, which occurs in neutrophils undergoing spontaneous apoptosis or triggered death by Fas. Taken together, PS-G elicitation of antiapoptotic effects on neutrophils primarily relies on activation of Akt-regulated signaling pathways.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 25 MEDLINE on STN DUPLICATE 8
 ACCESSION NUMBER: 2002193291 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11926309
 TITLE: CPPD crystal-induced suppression of neutrophil apoptosis is regulated by the ERK1/2 and PI3-kinase/Akt pathways.
 AUTHOR: Tudan C; Jackson J K; Burt H M
 CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.. tudanc@shaw.ca
 SOURCE: Inflammation research : official journal of the European Histamine Research Society ... [et al.], (2002 Feb) Vol. 51, No. 2, pp. 105-7.
 Journal code: 9508160. ISSN: 1023-3830.
 PUB. COUNTRY: Switzerland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200209
 ENTRY DATE: Entered STN: 4 Apr 2002
 Last Updated on STN: 28 Sep 2002
 Entered Medline: 27 Sep 2002

L5 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 ACCESSION NUMBER: 2003:52162 BIOSIS
 DOCUMENT NUMBER: PREV200300052162
 TITLE: Acquisition of an apoptotic phenotype by retinoic acid-matured HL-60 cells in PI3-kinase -dependent.
 AUTHOR(S): Jia, Song Hui [Reprint Author]; Parodo, Jean [Reprint Author]; Marshall, John C. [Reprint Author]
 CORPORATE SOURCE: Department of Surgery, University of Toronto, Toronto, ON, Canada
 SOURCE: Journal of Interferon and Cytokine Research, (2002) Vol. 22, No. Supplement 1, pp. S-156. print.
 Meeting Info.: Joint Meeting of the International Society for Interferon and Cytokine Research, the International Cytokine Society, the Society for Leukocyte Biology, and the European Cytokine Society on Cytokines and Interferons. Turin, Italy. October 06-10, 2002. International Society for Interferon and Cytokine Research.
 ISSN: 1079-9907 (ISSN print).
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 22 Jan 2003
 Last Updated on STN: 22 Jan 2003

L5 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:885681 CAPLUS
 DOCUMENT NUMBER: 136:31664

TITLE: Compositions and methods for identifying agents which modulate PTEN function and PI-3 kinase pathways

INVENTOR(S): Durden, Donald L.

PATENT ASSIGNEE(S): Advanced Research & Technology Institute, USA

SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 2001091699 | A2 | 20011206 | WO 2001-US17358 | 20010530 |
| WO 2001091699 | A3 | 20021227 | | |
| W: | | | | |
| AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: | | | | |
| GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2410514 | AA | 20011206 | CA 2001-2410514 | 20010530 |
| AU 2001065137 | A5 | 20011211 | AU 2001-65137 | 20010530 |
| US 2002150954 | A1 | 20021017 | US 2001-870379 | 20010530 |
| US 6777439 | B2 | 20040817 | | |
| EP 1289472 | A2 | 20030312 | EP 2001-939641 | 20010530 |
| R: | | | | |
| AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2005032727 | A1 | 20050210 | US 2003-712850 | 20031113 |
| US 2004142395 | A1 | 20040722 | US 2004-770725 | 20040203 |
| PRIORITY APPLN. INFO.: | | | US 2000-208437P | P 20000530 |
| | | | US 2001-274167P | P 20010308 |
| | | | US 2001-870379 | A1 20010530 |
| | | | WO 2001-US17358 | W 20010530 |
| AB | | | | |
| Methods are provided for the identification, biochem. characterization and therapeutic use of agents which impact PTEN, p53, PI-kinase and AKT mediated cellular signaling. The present invention provides methods for the treatment of cancer associated with PTEN mutation. Exemplary methods include delivery of a native PTEN encoding nucleic acid to cancer cells such that the native PTEN protein is expressed. Addnl. methods for the treatment of cancer in accordance with the present invention entail the administration of at least one agent selected from the group consisting of PTEN agonists, PI3 kinase inhibitors and AKT inhibitors. The aforementioned treatment protocols may also comprise the administration of conventional chemotherapeutic agents. In another aspect of the invention, methods for the prevention of aberrant angiogenesis are also provided. Methods for the administration of at least one agent selected from the group consisting of native PTEN encoding nucleic acids, PTEN agonists, PI3kinase inhibitors and AKT inhibitors for the inhibition or prevention of aberrant angiogenesis are also disclosed herein. PTEN has also been implicated in immunoreceptor modulation. Thus, in yet another aspect of the invention, methods for inhibiting the immune response in target cells are provided. In yet another aspect of the invention, methods for regulating p53 mediated gene expression are also provided. Such methods entail the administration of native PTEN, PTEN agonists and/or PI3 kinase inhibitors or AKT inhibitors to induce functional p53 in tumor cells. Given the widespread effects of PTEN, methods for identifying agents which modulate PTEN activity are also provided. Also provided in accordance with the present invention are high throughput screening methods for identifying small mols. which have affinity for PTEN or fragments thereof. | | | | |

L5 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:824537 CAPLUS
DOCUMENT NUMBER: 136:367504
TITLE: Bacterial lipoprotein activates nuclear factor kappa B and delays neutrophil apoptosis via a pathway involving p38 MAP kinase and PI3 kinase
AUTHOR(S): Manning, Brian J.; Wang, Jiang Huai; Redmond, H. Paul
CORPORATE SOURCE: Department of Academic Surgery, Cork University Hospital and University College Cork, Cork, Ire.
SOURCE: Surgical Forum (2001), 52, 167-168
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of bacterial lipoprotein (BLP) on neutrophil activation was examined by assessing nuclear factor kappa B activation and apoptotic rate over a 24-h period. The BLP activated NFkB in human neutrophils, and the time course of this activity was comparable to that of lipopolysaccharide, with maximal activation seen at 30 min. It also increased the nuclear translocation of the p65 subunit and induced a delay in apoptosis that was dependent on the p38 MAP kinase and the PI3 kinase pathways. NFkB inhibition and JNK inhibition did not affect the apoptotic rates of unstimulated neutrophils or of those treated with BLP. The inhibition of p38 MAP kinase also decreased the BLP-induced apoptotic delay assessed at 24 h to within normal limits.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> dis ibib abs l5 1-14

L5 ANSWER 1 OF 25 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2006045169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16223772
TITLE: Interaction between integrin alpha9beta1 and vascular cell adhesion molecule-1 (VCAM-1) inhibits neutrophil apoptosis.
AUTHOR: Ross Ewan A; Douglas Mike R; Wong See Heng; Ross Emma J; Curnow S John; Nash Gerard B; Rainger Ed; Scheel-Toellner Dagmar; Lord Janet M; Salmon Mike; Buckley Christopher D
CORPORATE SOURCE: Division of Immunity and Infection, Medical Research Council (MRC) Centre for Immune Regulation, Institute for Biomedical Research, University of Birmingham, United Kingdom.
SOURCE: Blood, (2006 Feb 1) Vol. 107, No. 3, pp. 1178-83.
Electronic Publication: 2005-10-13.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 26 Jan 2006
Last Updated on STN: 3 Mar 2006
Entered Medline: 2 Mar 2006

AB According to the prevailing paradigm, neutrophils are short-lived cells that undergo spontaneous apoptosis within 24 hours of their release from the bone marrow. However, neutrophil survival can be significantly prolonged within inflamed tissue by cytokines, inflammatory mediators, and hypoxia. During screening experiments aimed at identifying the effect of the adhesive

microenvironment on **neutrophil** survival, we found that VCAM-1 (CD106) was able to delay both spontaneous and Fas-induced **apoptosis**. VCAM-1-mediated survival was as efficient as that induced by the cytokine IFN-beta and provided an additive, increased delay in **apoptosis** when given in combination with IFN-beta. VCAM-1 delivered its antiapoptotic effect through binding the integrin alpha9beta1. The alpha9beta1 signaling pathway shares significant features with the IFN-beta survival signaling pathway, requiring PI3 kinase, NF-kappaB activation, as well as de novo protein synthesis, but the kinetics of NF-kappaB activation by VCAM-1 were slower and more sustained compared with IFN-beta. This study demonstrates a novel functional role for alpha9beta1 in **neutrophil** biology and suggests that adhesive signaling pathways provide an important extrinsic checkpoint for the resolution of inflammatory responses in tissues.

L5 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:78074 CAPLUS

DOCUMENT NUMBER: 142:172874

TITLE: Apoptosis-related kinase/G protein-coupled receptors and their use in diagnosis and drug screening

INVENTOR(S): Seery, Liam; Hayes, Ian; Murphy, Finbarr

PATENT ASSIGNEE(S): Eirx Therapeutics Limited, Ire.

SOURCE: U.S. Pat. Appl. Publ., 264 pp., Cont.-in-part of U.S. Ser. No. 764,238.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 2005019746 | A1 | 20050127 | US 2004-781581 | 20040218 |
| US 2004219616 | A1 | 20041104 | US 2004-764238 | 20040123 |
| PRIORITY APPLN. INFO.: | | | GB 2003-1566 | A 20030123 |
| | | | US 2003-457533P | P 20030325 |
| | | | US 2004-764238 | A2 20040123 |

AB The present invention relates to methods of identifying an agent that modulates the function of an **apoptosis**-associated polypeptide. RNA interference (siRNA knockdown) in the **neutrophil** model of **apoptosis** identify the following kinases and/or G protein-coupled receptors (GPCR) as having roles in **apoptosis**: MAK, GPR86, PCTAIRE, GRAF, MPSK1, RS6PK, TLK2, EK1, MKNK, NTKL, CDC42, RBSK, EDG6, PRK, MAPKK5, P14KB, FLT4, PSKH1, ITPKC, and ROCK. The invention also relates to methods of modulating **apoptosis**, diagnostic methods, arrays, kits and compns. based upon the **apoptosis**-associated polypeptides.

L5 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:487619 CAPLUS

DOCUMENT NUMBER: 143:171209

TITLE: Apoptotic Pathways Are Inhibited by Leptin Receptor Activation in **Neutrophils**

AUTHOR(S): Bruno, Andreina; Conus, Sebastien; Schmid, Ines; Simon, Hans-Uwe

CORPORATE SOURCE: Department of Pharmacology, University of Bern, Bern, Switz.

SOURCE: Journal of Immunology (2005), 174(12), 8090-8096

CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Leptin regulates food intake as well as metabolic, endocrine, and immune functions. It exerts proliferative and antiapoptotic activities in a variety of cell types, including T cells. Leptin also stimulates macrophages and neutrophils, and its production is increased during inflammation. In this study, we demonstrate that human neutrophils express leptin surface receptors under in vitro and in vivo conditions, and that leptin delays apoptosis of mature neutrophils in vitro. The antiapoptotic effects of leptin were concentration dependent and blocked by an anti-leptin receptor mAb. The efficacy

of leptin to block neutrophil apoptosis was similar to G-CSF. Using pharmacol. inhibitors, we obtained evidence that leptin initiates a signaling cascade involving PI3K- and MAPK-dependent pathways in neutrophils. Moreover, leptin delayed the cleavage of Bid and Bax, the mitochondrial release of cytochrome c and second mitochondria-derived activator of caspase, as well as the activation of both caspase-8 and caspase-3 in these cells. Taken together, leptin is a survival cytokine for human neutrophils, a finding with potential pathol. relevance in inflammatory diseases.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 25 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005205638 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15625305
TITLE: Activation of PI3-kinase/PKB
contributes to delay in neutrophil
apoptosis after thermal injury.
AUTHOR: Hu Zhihong; Sayeed Mohammed M
CORPORATE SOURCE: Dept. of Physiology, Loyola Univ. Medical Center, 2160 S.
First Ave., Maywood, IL 60153, USA.. zhul@luc.edu
CONTRACT NUMBER: R01GM-52325 (NIGMS)
R01GM-56865 (NIGMS)
SOURCE: American journal of physiology. Cell physiology, (2005 May)
Vol. 288, No. 5, pp. C1171-8. Electronic Publication:
2004-12-29.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 21 Apr 2005
Last Updated on STN: 10 Jun 2005
Entered Medline: 9 Jun 2005

AB Neutrophil apoptosis is delayed under trauma and/or sepsis injury conditions. The molecular mechanism for the delay in apoptosis has not been well defined. We investigated whether activation of phosphatidyl inositol 3-kinase (PI3-kinase)/PKB signaling pathway contributes to the delay in neutrophil apoptosis with thermal injury. Rats were subjected to burns (30% total body surface area, 98 degrees C for 10 s), and euthanized 24 h later. Blood neutrophils were isolated with the use of Ficoll gradient centrifugation and cultured for the indicated time periods. Apoptosis was determined using annexin V and PI labeling and flow cytometry. NF-kappaB activation was examined using gel mobility shift assay and confocal microscopy. Expression levels of inhibitory apoptosis proteins (IAPs), including cellular IAP1 (cIAP1), cIAP2, X-linked IAP (XIAP), and survivin, and Bcl-2 family members such as Bcl-x1 and Bad, were determined by Western blot analysis and/or RT-PCR, real-time PCR. The results showed that in culture, the decrease in apoptosis of neutrophils from thermally injured rats was prevented in the presence of PI3-kinase inhibitors wortmannin and LY-294002. There was upregulation of PKB and Bad

phosphorylation and NF-kappaB activation in N-formyl-1-methionyl-1-leucyl-1-phenylalanine-stimulated neutrophils from thermally injured rats compared with the sham injured group. Increased Bad phosphorylation and NF-kappaB activation were also attenuated by wortmannin. Bcl-x1 expression in neutrophils was upregulated with thermal injury and inhibited in the presence of wortmannin. However, the expression of IAP family members was neither affected by thermal injury nor inhibited by wortmannin. These data suggest that the delay in neutrophil apoptosis with thermal injury is partly caused by activation of PI3-kinase/PKB signaling and NF-kappaB, which appeared to be related to the increased Bcl-x1 expression and phosphorylation of Bad, but not IAP expression.

L5 ANSWER 5 OF 25 MEDLINE on STN DUPLICATE 3
 ACCESSION NUMBER: 2005222786 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15755871
 TITLE: The effect of fever-like temperatures on neutrophil signaling.
 AUTHOR: Salanova Birgit; Choi Mira; Rolle Susanne; Wellner Maren; Scheidereit Claus; Luft Friedrich C; Kettritz Ralph
 CORPORATE SOURCE: Medical Faculty of the Charite, Department of Nephrology and Hypertension, Franz Volhard Clinic at the Max Delbrück Center for Molecular Medicine, HELIOS-Klinikum-Berlin, Germany.
 SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2005 May) Vol. 19, No. 7, pp. 816-8. Electronic Publication: 2005-03-08.
 Journal code: 8804484. E-ISSN: 1530-6860.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200512
 ENTRY DATE: Entered STN: 29 Apr 2005
 Last Updated on STN: 23 Dec 2005
 Entered Medline: 22 Dec 2005

AB The effect of fever on neutrophils has not been explored. We tested the hypothesis that fever-like temperature spikes affect neutrophil signaling and function. Prior 60 min, 42 degrees C heat exposure inhibited p38 MAPK, ERK, PI3-Kinase/Akt, and NF-kappaB activation in TNF-alpha-challenged suspended neutrophils. Using pharmacological inhibitors and an inhibitory peptide transduced into neutrophils by a HIV-TAT sequence, we found that p38 MAPK and NF-kappaB mediate TNF-alpha-mediated delayed apoptosis in suspended neutrophils. Heat exposure (39-42 degrees C) did not affect constitutive apoptosis but abrogated TNF-alpha-delayed apoptosis in these suspended cells. In contrast, adhesion-dependent functions were not inhibited. Furthermore, we found that heat exposure neither blocked p38 MAPK, ERK, and NF-kappaB activation in neutrophils on fibronectin nor prevented delayed apoptosis by TNF-alpha when cells interacted with fibronectin. Above and beyond apoptosis, TNF-alpha initiated NF-kappaB-dependent gene transcription. Heat exposure blocked this effect in suspended neutrophils but not in neutrophils on fibronectin. Finally, we show that beta2-integrins, which are not necessary for TNF-alpha-induced NF-kappaB activation at 37 degrees C, transduce costimulatory signals allowing NF-kappaB activation after heat exposure. The effect could protect circulating neutrophils from TNF-alpha activation, while not interfering with activation of adherent neutrophils. Fever could make neutrophils more parsimonious.

L5 ANSWER 6 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2005670483 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 16306804
 TITLE: Cardioprotection with adenosine A2 receptor activation at reperfusion.
 AUTHOR: Xu Zhelong; Mueller Robert A; Park Sung-Sik; Boysen Philip G; Cohen Michael V; Downey James M
 CORPORATE SOURCE: Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA..
 zxu@aims.unc.edu
 CONTRACT NUMBER: HL-20648 (NHLBI)
 HL-50688 (NHLBI)
 SOURCE: Journal of cardiovascular pharmacology, (2005 Dec) Vol. 46, No. 6, pp. 794-802. Ref: 83
 Journal code: 7902492. ISSN: 0160-2446.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200512
 ENTRY DATE: Entered STN: 21 Dec 2005
 Last Updated on STN: 29 Dec 2005
 Entered Medline: 28 Dec 2005

AB Pre-ischemic treatment is seldom possible in the clinical setting of acute myocardial infarction. Thus, to successfully save myocardium from infarction, it is required that protective interventions must be effective when applied after ischemia has begun or at the onset of reperfusion. Unfortunately, in spite of a large body of experimental data showing that various interventions are cardioprotective at reperfusion, no specific therapy has yet been established to be clinically applicable. However, recent data from several laboratories have shown that adenosine and its analogues given at reperfusion can markedly protect the heart from ischemia/reperfusion injury. While the experimental data suggest that factors such as adenosine A2 receptor activation, anti-neutrophil effect, attenuation of free radical generation, increased nitric oxide (NO) availability, activation of the PI3-kinase/Akt pathway and ERK, prevention of mitochondrial damage, and anti-apoptotic effects may be involved in the protective effect of adenosine or its analogues, the exact receptor subtype(s), the detailed signaling mechanisms, and interaction between those individual factors are still unknown. A definite answer to these unsolved problems will offer insights into the mechanisms of cardioprotection at reperfusion, and will be critical for developing a successful therapeutic strategy to salvage ischemic myocardium in patients with acute myocardial infarction.

L5 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:417048 CAPLUS
 DOCUMENT NUMBER: 143:90811
 TITLE: Clozapine prevents apoptosis and enhances receptor-dependent respiratory burst in human neutrophils
 AUTHOR(S): Vargas, F.; Rivas, C.; Perdomo, H.; Rivas, A.; Ojeda, L. E.; Velasquez, M.; Correia, H.; Hernandez, A.; Fraile, G.
 CORPORATE SOURCE: Laboratorio de Fotoquimica, Facultad de Ciencias de la Salud, Universidad de Carabobo-Nucleo Aragua, Venez.
 SOURCE: Pharmazie (2005), 60(5), 364-368
 CODEN: PHARAT; ISSN: 0031-7144
 PUBLISHER: Govi-Verlag Pharmazeutischer Verlag GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The present study was undertaken to determine if the antipsychotic drug clozapine (CLZ) in the concentration range 2-50 μ M can rescue polymorphonuclear cells (PMNs) from undergoing apoptosis

. Our results indicate that 20 μ M CLZ can rescue PMNs both from UVB-accelerated (28.0% vs. 45.9% for control without CLZ; $P < 0.05$) and from spontaneous (35.8% vs. 57.6%; $P < 0.05$) apoptosis whereas 50 μ M CLZ could rescue PMNs from spontaneous (34.3% vs. 57.6%; $P < 0.05$) apoptosis only. Furthermore, since apoptosis has been reported to involve the impairment of PMN function, we evaluated the effects of CLZ on respiratory burst in UVB-irradiated and in unirradiated PMNs. When 20 or 50 μ M CLZ-pretreated PMNs were aged in a culture during 4 h, the luminol-dependent chemiluminescence (CL) response was 3-fold ($P < 0.01$) and 2.5-fold ($P < 0.05$) increased, resp., by subsequent exposure to serum opsonized zymosan (OZ). When 50 μ M-pretreated PMNs were either UVB-irradiated or unirradiated, the CL response was 2.6-fold ($P < 0.05$) and 3.3-fold ($P < 0.05$) increased, resp., after subsequent exposure to formyl-methionyl-leucyl-phenylalanine (fMLP). In contrast, the degree of enhancement was negligible upon subsequent exposure to ionomycin or phorbol myristate acetate (PMA). When incubation times were extended up to 22 h, the CL response induced by OZ in 20 μ M CLZ-treated PMNs had a 4.9-fold increase ($P < 0.001$). This priming effect could be reverted when 20 μ M CLZ-treated PMNs (aged 4 h in culture) were coincubated for 5 min with the protein tyrosine kinase inhibitor genistein as well as with the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin. These findings suggest that CLZ primes respiratory burst and prevents PMN apoptosis as a consequence of tyrosine phosphorylation- and PI3-K activation-dependent signal transduction pathways.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 25 MEDLINE on STN DUPLICATE 4
 ACCESSION NUMBER: 2005328015 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15793629
 TITLE: Postconditioning--A new link in nature's armor against myocardial ischemia-reperfusion injury.
 AUTHOR: Vinten-Johansen J; Zhao Z-Q; Zatta A J; Kin H; Halkos M E; Kerendi F
 CORPORATE SOURCE: The Cardiothoracic Research Laboratory, Carlyle Fraser Heart Center, 550 Peachtree Street N.E., Atlanta, Georgia 30308-2225, USA.. jvinten@emory.edu
 CONTRACT NUMBER: HL069487 (NHLBI)
 SOURCE: HL64886 (NHLBI)
 SOURCE: Basic research in cardiology, (2005 Jul) Vol. 100, No. 4, pp. 295-310. Electronic Publication: 2005-03-30. Ref: 105
 Journal code: 0360342. ISSN: 0300-8428.
 PUB. COUNTRY: Germany: Germany, Federal Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200510
 ENTRY DATE: Entered STN: 28 Jun 2005
 Last Updated on STN: 12 Oct 2005
 Entered Medline: 11 Oct 2005
 AB Reperfusion injury is a complex process involving several cell types (endothelial cells, neutrophils, and cardiomyocytes), soluble proinflammatory mediators, oxidants, ionic and metabolic dyshomeostasis, and cellular and molecular signals. These participants in the pathobiology of reperfusion injury are not mutually exclusive. Some of these events take place during the very early moments of reperfusion, while others, seemingly triggered in part by the early events, are activated within a later timeframe. Postconditioning is a series of brief mechanical interruptions of reperfusion following a specific prescribed algorithm applied at the very onset of reperfusion. This algorithm lasts only from 1 to 3 minutes depending on species. Although associated with

re-occlusion of the coronary artery or re-imposition of hypoxia in cell culture, the reference to ischemia has been dropped. Postconditioning has been observed to reduce infarct size and apoptosis as the "end games" in myocardial therapeutics; salvage of infarct size was similar to that achieved by the gold standard of protection, ischemic preconditioning. The cardioprotection was also associated with a reduction in: endothelial cell activation and dysfunction, tissue superoxide anion generation, neutrophil activation and accumulation in reperfused myocardium, microvascular injury, tissue edema, intracellular and mitochondrial calcium accumulation. Postconditioning sets in motion triggers and signals that are functionally related to reduced cell death. Adenosine has been implicated in the cardioprotection of postconditioning, as has e-NOS, nitric oxide and guanylyl cyclase, opening of K(ATP) channels and closing of the mitochondrial permeability transition pore. Cardioprotection by postconditioning has also been associated with the activation of intracellular survival pathways such as ERK1/2 and PI3 kinase - Akt pathways. Other pathways have yet to be identified. Although many of the pathways involved in postconditioning have also been identified in ischemic preconditioning, some may not be involved in preconditioning (ERK1/2). The timing of action of these pathways and other mediators of protection in postconditioning differs from that of preconditioning. In contrast to preconditioning, which requires a foreknowledge of the ischemic event, postconditioning can be applied at the onset of reperfusion at the point of clinical service, i.e. angioplasty, cardiac surgery, transplantation.

L5 ANSWER 9 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 ACCESSION NUMBER: 2006:222745 BIOSIS
 DOCUMENT NUMBER: PREV200600221732
 TITLE: Expression and distribution of signal regulatory protein alpha in human neutrophils.
 AUTHOR(S): Stenberg, Asa [Reprint Author]; Oldenberg, Anna; Frazier, William A.; Sehlin, Janove; Oldenberg, Per-Arne
 CORPORATE SOURCE: Umea Univ, Dept Integr Med Biol, SE-90187 Umea, Sweden
 SOURCE: Journal of Leukocyte Biology, (2005) No. Suppl. S, pp. 37-38.
 Meeting Info.: 38th Annual Meeting of the Society-for-Leukocyte-Biology. Oxford, ENGLAND. September 21 -24, 2005. Soc Leukocyte Biol.
 CODEN: JLBIE7. ISSN: 0741-5400.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 5 Apr 2006
 Last Updated on STN: 5 Apr 2006

L5 ANSWER 10 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
 ACCESSION NUMBER: 2005185855 EMBASE
 TITLE: Activation of PI3-kinase/PKB contributes to delay in neutrophil apoptosis after thermal injury.
 AUTHOR: Hu Z.; Sayeed M.M.
 CORPORATE SOURCE: Z. Hu, Dept. of Physiology, Loyola Univ. Medical Center, 2160 S. First Ave., Maywood, IL 60153, United States. zhul@luc.edu
 SOURCE: American Journal of Physiology - Cell Physiology, (2005) Vol. 288, No. 5 57-5, pp. C1171-C1178. .
 Refs: 43
 ISSN: 0363-6143 CODEN: AJPCDD
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 002 Physiology
 LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2005
Last Updated on STN: 19 May 2005

AB Neutrophil apoptosis is delayed under trauma and/or sepsis injury conditions. The molecular mechanism for the delay in apoptosis has not been well defined. We investigated whether activation of phosphatidyl inositol 3-kinase (PI3-kinase)/PKB signaling pathway contributes to the delay in neutrophil apoptosis with thermal injury. Rats were subjected to burns (30% total body surface area, 98°C for 10 s), and euthanized 24 h later. Blood neutrophils were isolated with the use of Ficoll gradient centrifugation and cultured for the indicated time periods. Apoptosis was determined using annexin V and PI labeling and flow cytometry. NF-κB activation was examined using gel mobility shift assay and confocal microscopy. Expression levels of inhibitory apoptosis proteins (IAPs), including cellular IAP1 (cIAP1), cIAP2, X-linked IAP (XIAP), and survivin, and Bcl-2 family members such as Bcl-xl and Bad, were determined by Western blot analysis and/or RT-PCR, real-time PCR. The results showed that in culture, the decrease, in apoptosis of neutrophils from thermally injured rats was prevented in the presence of PI3-kinase inhibitors wortmannin and LY-294002. There was upregulation of PKB and Bad phosphorylation and NF-κB activation in N-formyl-L-methionyl-L-leucyl-L-phenylalanine-stimulated neutrophils from thermally injured rats compared with the sham injured group. Increased Bad phosphorylation and NF-κB activation were also attenuated by wortmannin. Bcl-xl expression in neutrophils was upregulated with thermal injury and inhibited in the presence of wortmannin. However, the expression of IAP family members was neither affected by thermal injury nor inhibited by wortmannin. These data suggest that the delay in neutrophil apoptosis with thermal injury is partly caused by activation of PI3-kinase/PKB signaling and NF-κB, which appeared to be related to the increased Bcl-xl expression and phosphorylation of Bad, but not IAP expression. Copyright .COPYRG. 2005 the American Physiological Society.

L5 ANSWER 11 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:235909 BIOSIS
DOCUMENT NUMBER: PREV200510020974
TITLE: The effect of fever-like temperatures on neutrophil signaling.
AUTHOR(S): Salanova, Birgit; Choi, Mira; Rolle, Susanne; Wellner, Maren; Scheidereit, Claus; Luft, Friedrich C.; Kettritz, Ralph [Reprint Author]
CORPORATE SOURCE: Wiltbergstr 50, D-13125 Berlin, Germany
kettritz@fvk.charite-buch.de
SOURCE: FASEB Journal, (MAR 2005) Vol. 19, No. 3.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005

AB The effect of fever on neutrophils has not been explored. We tested the hypothesis that fever-like temperature spikes affect neutrophil signaling and function. Prior 60 min, 42 degrees C heat exposure inhibited p38 MAPK, ERK, PI3-Kinase/Akt, and NF-kappa B activation in TNF-alpha-challenged suspended neutrophils. Using pharmacological inhibitors and an inhibitory peptide transduced into neutrophils by a HIV-TAT sequence, we found that p38 MAPK and NF-kappa B mediate TNF-alpha-mediated delayed apoptosis in suspended neutrophils. Heat exposure (39-42 degrees C) did not affect constitutive apoptosis but abrogated TNF-alpha-delayed apoptosis in these suspended cells.

In contrast, adhesion-dependent functions were not inhibited. Furthermore, we found that heat exposure neither blocked p38 MAPK, ERK, and NF-kappa B activation in neutrophils on fibronectin nor prevented delayed apoptosis by TNF-alpha. when cells interacted with fibronectin. Above and beyond apoptosis, TNF-alpha initiated NF-kappa B-dependent gene transcription. Heat exposure blocked this effect in suspended neutrophils but not in neutrophils on fibronectin. Finally, we show that beta 2-integrins, which are not necessary for TNF-alpha-induced NF-kappa B activation at 37 degrees C, transduce costimulatory signals allowing NF-kappa B activation after heat exposure. The effect could protect circulating neutrophils from TNF-alpha. activation, while not interfering with activation of adherent neutrophils. Fever could make neutrophils more parsimonious.

L5 ANSWER 12 OF 25 MEDLINE on STN DUPLICATE 5
 ACCESSION NUMBER: 2004262919 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15162444
 TITLE: The survival effect of TNF-alpha in human neutrophils is mediated via NF-kappa B-dependent IL-8 release.
 AUTHOR: Cowburn Andrew S; Deighton John; Walmsley Sarah R; Chilvers Edwin R
 CORPORATE SOURCE: Respiratory Medicine Division, Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, GB.. asc32@hermes.cam.ac.uk
 SOURCE: European journal of immunology, (2004 Jun) Vol. 34, No. 6, pp. 1733-43. Journal code: 1273201. ISSN: 0014-2980.
 PUB. COUNTRY: Germany: Germany, Federal Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200407
 ENTRY DATE: Entered STN: 27 May 2004
 Last Updated on STN: 30 Jul 2004
 Entered Medline: 29 Jul 2004

AB The capacity of cytokines to modulate neutrophil apoptosis is thought to be a major factor influencing the resolution of granulocytic inflammation. We have previously shown that the late survival effect of TNF-alpha in human neutrophils involves activation of both NF-kappa B and phosphoinositide 3-kinase (PI3-kinase) pathways. In this study, we address how these pathways integrate to prevent cell death. In human neutrophils, TNF-alpha (200 U/ml) induced rapid I kappa B-alpha degradation, NF-kappa B activation and IL-8 release (31.8+/-5.4 pg/10(5) cells/2 h), whereas GM-CSF (10 ng/ml) stimulated an equivalent IL-8 release (26.5+/-4.5 pg/10(5) cells/2 h) without enhanced I kappa B-alpha degradation or NF-kappa B activation compared to control. Importantly, inhibition of PI3-kinase did not modify TNF-alpha -induced I kappa B-alpha degradation, yet fully inhibited the survival effect of both cytokines. Inhibition of I kappa B-alpha phosphorylation, PI3-kinase or ERK1/2 activation blocked IL-8 release by both cytokines. Blocking IL-8 activity by inhibiting its synthesis or by using a neutralizing antibody enhanced the early pro-apoptotic effect of TNF-alpha and inhibited its late survival effect without affecting GM-CSF-induced survival. These data suggest that cross-talk between NF-kappa B and PI3-kinase pathways in TNF-alpha -stimulated neutrophils results from NF-kappa B/ERK1/2-dependent IL-8 production which acts in an autocrine manner to drive PI3-kinase-dependent survival. In contrast, GM-CSF-mediated survival does not involve NF-kappa B activation or IL-8 release.

L5 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:458242 CAPLUS

DOCUMENT NUMBER: 141:223482

TITLE: The importance of resolution of inflammation in the pathogenesis of ANCA-associated vasculitis

AUTHOR(S): Harper, L.; Williams, J. M.; Savage, C. O.

CORPORATE SOURCE: Division of Medical Sciences, University of Birmingham, Birmingham, B15 2TT, UK

SOURCE: Biochemical Society Transactions (2004), 32(3), 502-506

CODEN: BCSTB5; ISSN: 0300-5127

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The primary small-vessel systemic vasculitides are disorders that target small blood vessels, inducing vessel wall inflammation, and are associated with the development of anti-neutrophil cytoplasmic antibodies. Multiple organs are attacked, including the lungs and kidneys. Increasing knowledge of pathogenesis suggests that the antibodies activate neutrophils inappropriately, leading to endothelial and vascular damage. Cytokines, such as tumor necrosis factor, can facilitate damage by priming the neutrophils and activating endothelial cells. Apoptosis of infiltrating neutrophils is also disrupted by anti-neutrophil cytoplasmic antibody activation, and removal of these effete cells occurs in a pro-inflammatory manner, promoting persistent inflammation. The autoimmune response may be promoted by aberrant phagocytosis of apoptotic neutrophils by dendritic cells. Understanding the pathogenesis can help to rationalize existing therapies and indicate new approaches to therapy.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:458233 CAPLUS

DOCUMENT NUMBER: 141:223910

TITLE: Gene profiling of in vitro and in vivo models of delayed neutrophil apoptosis: a common pathway?

AUTHOR(S): O'Neill, A.; Greenan, M. C.; Doyle, B.; Fitzpatrick, J. M.; Watson, R. W. G.

CORPORATE SOURCE: Department of Surgery, Conway Institute, University College Dublin, Mater Misericordiae University Hospital, Dublin, 7, Ire.

SOURCE: Biochemical Society Transactions (2004), 32(3), 470-473

CODEN: BCSTB5; ISSN: 0300-5127

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mechanisms responsible for the termination of an inflammatory response include the activation of a genetic program of cellular suicide termed apoptosis, which leads to the elimination of the cellular effectors of acute inflammation, particularly the neutrophil. However, delays in this response result in the persistence of inflammation and the development of inflammatory disorders. Understanding the mechanism that inhibits the process of cell death may be helpful in the treatment of inflammatory disorders. Inflammatory cytokines have been shown to inhibit apoptosis through stabilization of the mitochondria and inhibition of the caspase cascade. To date, how these processes are inhibited remains the central question. The authors hypothesize that the decision for the delay in neutrophil apoptosis is made through signals delivered on the cell surface, which activate combinations of specific genes that inhibit the cell death

pathway. Gene chip microarray expts. were performed in in vivo and in vitro models of delayed neutrophil apoptosis. Anal. has yielded changes in a large number of genes involved in inflammation, metabolism, signaling, mitochondrial function and apoptosis. A number of genes have been identified as suitable targets responsible for the regulation of neutrophil apoptosis and their expression was confirmed by real-time PCR and explored at the level of the protein. Their functional role in the apoptotic response is now being determined. One significant finding is that the gene patterns of delay in vitro and in vivo appear to be different, indicating the possibility for different pathways regulating the delay in neutrophil apoptosis.

REFERENCE COUNT:

23

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